

Original Research

Use of Neo-melubrina, a banned antipyretic drug, in San Diego, California: a survey of patients and providers

ABSTRACT ● **Background** Dipyrrone is an antipyretic drug that has been associated with agranulocytosis. It is banned in the United States but is available in Mexico under the name Neo-melubrina. ● **Objectives** To define the use of Neo-melubrina in the Hispanic population of 2 San Diego, California, community clinics and to determine local physicians' and nurse practitioners' awareness of the drug and its risks. ● **Design** Patient survey and provider survey. ● **Participants** Patients: 200 parents of Hispanic pediatric patients. Providers: members of San Diego chapters of the American Academy of Pediatrics, the American Academy of Family Physicians, and the California Coalition of Nurse Practitioners. ● **Main outcome measures** Self-reported use of Neo-melubrina by patients, and provider awareness of Neo-melubrina and its most significant side effects. ● **Results** Of the 200 patients, 76 (38.0%) reported a lifetime use of Neo-melubrina. Most (56%) used it for both pain and fever. Most providers were unable to correctly identify why Neo-melubrina might be used or its adverse effects. Physicians answered correctly more often than nurse practitioners and pediatric providers more often than family medicine providers. Providers who trained within 75 miles of the US-Mexico border, who reported a patient population of more than 50% Hispanic, and who were resident physicians at the time of the survey were most likely to answer correctly. ● **Conclusions** Neo-melubrina has been used by a substantial percentage of Hispanic patients in the community clinics surveyed. Many San Diego health care providers are unaware of this medication and may, therefore, miss opportunities to educate patients about safer alternatives.

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Medical practice along an international border can pose unique challenges to health care providers. In San Diego, California, the proximity of the US-Mexico border offers local residents access to medical treatments and pharmacologic therapeutics not always approved in the United States.¹ The purchase of medications at Mexican pharmacies without a physician's prescription may be viewed by patients as inexpensive and convenient; however, this practice can place the patient at risk for serious medical complications.² Providers must be aware of commonly used foreign medications so that they can appropriately counsel patients and identify side effects.

Dipyrrone (also known as metamizole) is an effective analgesic and antipyretic drug used in Europe and Latin America.³ It was banned in the United States by the Food and Drug Administration (FDA) in 1977 because it is known to induce agranulocytosis.⁴⁻⁸ Because the drug remains available over the counter (OTC) in many countries, including Mexico, domestic cases of dipyrrone-induced agranulocytosis continue to occur.^{9,10} Dipyrrone is commonly marketed as a stronger form of aspirin and is often referred to as the "Mexican aspirin."¹⁰ It is sold in Mexico primarily under the name Neo-melubrina.

The actual rate of agranulocytosis following dipyrrone use is difficult to quantify, and studies that examine this incidence use different measures of risk. In the 1986 International Agranulocytosis and Aplastic Anemia Study, dipyrrone was the drug found to be most commonly associated with agranulocytosis.⁵ Regional differences ex-

Summary points

- Despite that the antipyretic dipyrrone has been banned in the United States since 1977 because of its association with agranulocytosis, it continues to be sold over the counter in Mexico under the brand name Neo-melubrina
- Although 38% of Hispanic patients at a San Diego community clinic report having used dipyrrone, most San Diego health care providers are unaware of the medication and its risks
- More education is needed so that providers can adequately evaluate and counsel patients regarding over-the-counter medication use

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None declared

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isted, with the estimated excess risk of agranulocytosis for any dipyrrone exposure in a 1-week period ranging from 1.1 per million in Germany and Spain to 0.2 per million in Israel and Budapest. Other authors have found higher risks; for example, Böttiger and Westerholm suggested that agranulocytosis occurs in about 1 in 3,000 dipyrrone users¹¹; the validity of this study has been called into question, however.⁵ Whether agranulocytosis occurs more or less frequently in children than in adults is not clear.

We are unaware of any studies examining the prevalence of dipyrrone use or provider knowledge of the medication. To address these issues, we surveyed Hispanic patients of 2 local community clinics regarding their lifetime use of dipyrrone. In addition, we surveyed pediatricians, family physicians, and nurse practitioners in San Diego

about their awareness of Neo-melubrina use. We also gathered information on a variety of provider demographic variables in an attempt to best target additional educational efforts.

DESIGN

This study is based on 2 cross-sectional surveys, both approved by the Institutional Review Board of the University of California, San Diego.

Patient survey

Between June 1998 and January 1999, patient data were collected in 2 San Diego community clinics with large Hispanic populations. All patients were uninsured or receiving Medicaid. Funding limited patient enrollment to 100 per clinic. Parents of Hispanic patients aged 1 to 12 years presenting to the clinic for either a well-care or a sick visit were asked to participate by completing a survey regarding the use of OTC antipyretic medications. Clinic staff approached consecutive patients presenting to the clinic on study days about participation in the study. Ethnicity was determined by the code entered by the parent on the clinic registration form. Parents who had previously participated were excluded. After verbal informed consent was obtained, a Spanish-speaking medical assistant or physician verbally administered the survey. After completion of the survey, all parents received verbal education regarding the risks associated with dipyrone use. In addition, as compensation for participation, they received a sample of acetaminophen (donated by McNeil Pharmaceuticals) with dosing instructions.

To reduce reporting bias, the patient survey focused on the use of acetaminophen, ibuprofen, and dipyrone with equal emphasis. These medications were identified by generic and brand names. Initially, participants were asked what was their first-choice medication for fever for themselves or their family. They were then asked if they had ever used each of the above 3 medications for themselves or their family. When a positive response was obtained, they were questioned regarding the frequency of use of the medication and the symptoms for which it is used.

Provider survey

The provider component of the study consisted of a 1-page questionnaire that was mailed to 1998 members of the San Diego chapters of the American Academy of Pediatrics, American Academy of Family Physicians, and the California Coalition of Nurse Practitioners. Information regarding provider demographic characteristics included academic degree, specialty, type of practice, location of residency or training program, provider's ability to speak Spanish, and estimated percentage of Hispanic patients seen in clinical practice. Provider awareness of Neo-

melubrina was determined by the use of fill-in questions regarding symptoms for which the product is used ("indications") and serious adverse effects. Correct responses for the indications question were determined by consulting the 1974 *Physicians' Desk Reference (PDR)*, which lists fever as the indication for the use of dipyrone.¹² Pain was added as an acceptable response because this is a frequent reason for use given by patients. Therefore, acceptable responses included fever, antipyretic, elevated temperature, headache, arthritis, and pain. Correct responses for "most serious adverse effect" were also determined by consulting the 1974 PDR, which lists fatal agranulocytosis as the most serious adverse effect.¹² Responses related to agranulocytosis, such as neutropenia, aplastic anemia, agranulocytosis, bone marrow suppression, pancytopenia, aplastic crisis, granulocytopenia, and leukopenia, were all scored as correct. Partially or nearly correct answers such as blood problems, blood dyscrasias, anemia, death, toxicity, and thrombocytopenia were also scored as correct.

After all surveys were received, a brief "Neo-melubrina fact sheet" was mailed to all 1,358 providers on the original mailing list. This fact sheet contained information about the drug itself, the incidence of adverse effects, symptoms and treatment of agranulocytosis, and recommendations for providers.

RESULTS

Patient responses

A total of 200 parents were enrolled, 100 from each clinic. No parent refused participation. Of these 200 participants, 184 (92.0%) listed Tylenol or Tempa as their first-choice medication for fever, 7 (3.5%) listed Motrin, and 9 (4.5%) listed Neo-melubrina. When questioned whether they had ever used a medication for themselves or their family, 199 (99.5%) had used acetaminophen, 53 (26.5%) had used ibuprofen, and 76 (38.0%) had used dipyrone or Neo-melubrina.

Most patients who use dipyrone do so less than 3 times per month (table 1). Reasons for using dipyrone included pain (7/75 [9.3%]), fever (25/75 [33.3%]), and both pain and fever (42/75 [56.0%]). One participant responded "don't know," and another failed to respond.

Provider responses

A total of 1,358 questionnaires were mailed to 492 family practice physicians, 578 pediatricians, and 288 nurse practitioners. Two hundred twenty-six pediatricians (39%), 162 family physicians (33%), and 147 nurse practitioners (51%) responded, for a total of 535 (a response rate of 39.4%). Partially completed questionnaires were analyzed only for those questions answered.

Provider demographics are listed in table 2. Of the providers who identified their specialty as "other," all were

Table 1 Patient survey results: reported frequency of use of various antipyretic or analgesic medications

Frequency of use, times/mo	Aceta-minophen (n = 199), no. (%)	Ibuprofen (n = 53), no. (%)	Dipyrone (n = 76), no. (%)
0 to 3	148 (74)	38 (72)	60 (79)
4 to 10	13 (6)	2 (4)	1 (1)
>10	1 (1)	0	0
Don't know	33 (17)	8 (15)	13 (17)
Did not respond	4 (2)	5 (9)	2 (3)

nurse practitioners with clinical practice in areas of women's health, geriatrics, surgery, anesthesia, and internal medicine.

Table 3 shows the percentage of respondents by demographic characteristics who answered knowledge ques-

Table 2 Provider demographic characteristics

Demographic	Provider, no. (%)
Academic degree (n = 535)	
MD or DO	389 (72.7)
NP	146 (27.3)
Specialty (n = 478)	
Family medicine	229 (47.9)
Pediatrics	237 (49.6)
Other*	12 (2.5)
Type of practice (n = 528)	
Private practice	112 (21.2)
Group or HMO	211 (40.0)
Community clinic	52 (9.8)
Residency	23 (4.4)
Not currently practicing	34 (6.4)
Other	96 (18.2)
Location of training by distance from US-Mexico border (n = 466), mi	
0-75	218 (46.8)
76-150	69 (14.8)
>150	179 (38.4)
Ability to speak Spanish (n = 527)	
None	59 (11.2)
Very little	219 (41.6)
Moderate	168 (31.9)
Fluent	63 (12.0)
Native speaker	18 (3.4)
Estimated percentage of Hispanic patients in clinical practice (n = 417)	
<25%	229 (54.9)
25% to <50%	117 (28.1)
50% to 75%	51 (12.2)
>75%	20 (4.8)

MD = doctor of medicine; DO = doctor of osteopathy; NP = nurse practitioner; HMO = health maintenance organization
 Other comprised nurse practitioners specializing in women's health, geriatrics, surgery, anesthesia, and internal medicine.

tions correctly. More than 70% of physicians did not know the indications or adverse effects associated with Neo-melubrina use.

The location of training varied across 31 states, Mexico (n=1), and Canada (n=2). A breakpoint of 75 miles from the US-Mexico border was chosen for analysis because this range includes training programs within San Diego County.

Figure 1 depicts provider knowledge by type of practice. Sixty-five percent of resident physicians and 40% of community clinic providers responded correctly to questions regarding symptoms.

DISCUSSION

That 38.0% of Hispanic parents in a community clinic population have used Neo-melubrina for themselves or their family is striking. Although we found that lifetime Neo-melubrina use was frequent, most participants, even those who had used Neo-melubrina, selected Tylenol as their first-choice medication for fever. It is unclear, then, why patients might use Neo-melubrina under some circumstances. Possible explanations include ease of attainment, cost, or familial influence. Further study would help to clarify these issues. Most patients who use dipyrone do so for fever, and thus, physicians should have a heightened awareness of OTC medication use in Hispanic patients when fever is a presenting symptom.

According to our survey results, a relatively large proportion of San Diego health care providers are unaware of the medication Neo-melubrina, the symptoms for which it is used, and its attendant risks. In general, providers in most demographic groups were considerably more aware of indications for the use of Neo-melubrina than of its adverse effects.

Differences in awareness observed between many of the groups of providers may reflect a difference in the content of training programs or, alternatively, a difference in clinical experience. For example, because they tend to care for more complicated patients than do nurse practitioners, physicians may be more likely to be involved in the care of a patient who has suffered an adverse event related to Neo-melubrina use, which would then raise awareness of this product.

Pediatric providers were more likely than family medicine providers to be aware of Neo-melubrina. The medical literature is unclear as to whether children are equally vulnerable to the adverse effects of Neo-melubrina. If children are, in fact, more susceptible, then those who care primarily for children would be encountering patients with adverse effects more frequently.

Knowledge of indications for Neo-melubrina use increased with increased provider fluency in Spanish. This may be indicative of increased knowledge of cultural be-

Table 3 Providers who correctly answered questions regarding indications for and adverse effects of Neo-melubrina use

Demographic characteristic*	Providers' knowledge, no. (%)	
	Indications	Adverse effects
Academic degree		
MD or DO (n = 385)	108 (28.1)	81 (21.0)
NP (n = 145)	11 (7.6)	7 (4.8)
Specialty		
Family medicine (n = 227)	21 (9.2)	8 (3.5)
Pediatrics (n = 235)	95 (40.4)	77 (32.8)
Other (n = 12)	0	0
Ability to speak Spanish		
None (n = 59)	4 (6.8)	7 (11.9)
Very little (n = 218)	34 (15.6)	31 (14.2)
Moderate (n = 168)	39 (23.2)	28 (16.7)
Fluent (n = 63)	26 (41.3)	16 (25.4)
Native speaker (n = 18)	15 (83.3)	5 (27.8)
Estimated percentage of Hispanic patients in clinical practice		
≤50% (n = 345)	68 (19.7)	55 (15.9)
>50% (n = 71)	324 (5.1)	19 (26.8)
Location of training by distance from US-Mexico border, mi		
≤75 (n = 217)	67 (30.9)	57 (26.3)
>75 (n = 247)	49 (19.8)	30 (12.1)

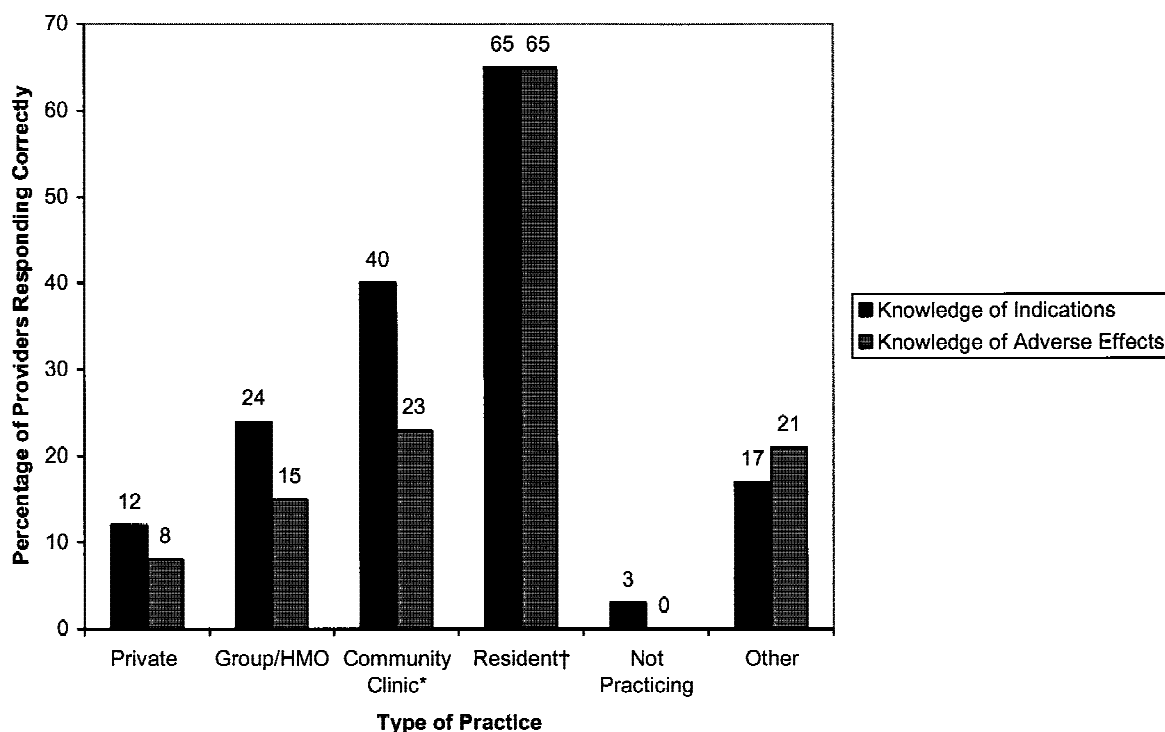
*Total numbers for each category vary because provider did not respond to the question or the question was not applicable to the respondent.

haviors and habits that come with an improved ability to communicate with Spanish-speaking patients. The native Spanish speakers may have a firsthand familiarity with Neo-melubrina and its indications, perhaps through the use of this medication among their own friends and family.

Although resident physicians represented only a small proportion of the study population, their level of awareness was the highest. This could reflect in part that those in training spend more time in the hospital setting than do community providers and, therefore, are more likely to have recent experience with patients having complications of Neo-melubrina use. This may also explain why residents had an equal awareness of indications for and adverse effects of Neo-melubrina, whereas community clinic providers had greater awareness of indications than of adverse effects.

Only 17% of responding providers reported having more than 50% Hispanic patients. If Neo-melubrina use is limited to Hispanic patients, then this subgroup of providers would have the greatest need for knowledge of this medication. However, non-Hispanic patients may prefer to obtain medications in Mexico because of cost or because of perceived increased effectiveness. Investigation into the use of Neo-melubrina by other patient populations is clearly warranted.

Our study has several limitations. We did not differ-



Knowledge of indications by practice type. Asterisk indicates $P \leq 0.05$ for community clinic providers compared with every other type of provider for knowledge of indications only. Dagger indicates $P \leq 0.05$ for residents compared with every other type of provider for knowledge of both indications and adverse effects.

entiate between lifetime, recent, or current use of dipyrone. In the patient survey, participants were asked to recall the use of medications by name. If a patient used a medication given to them by a friend or a pharmacist, without taking note of the product's name, he or she would then have a difficult time identifying this medication in our survey. The potential for recall bias exists because a lifetime use of the drug could include use during childhood. In addition, patients may be reluctant to report the use of medication obtained in Mexico. We attempted to avoid this by identifying acetaminophen by brand names sold both in the United States and in Mexico and also by shifting the focus away from dipyrone so that parents were questioned about all 3 OTC antipyretic medications. In the provider survey, the study sample was limited to members of the professional organizations whose mailing lists were used. Therefore, participants in this study may not have been representative of all providers in San Diego. Also, the potential exists for nonresponder bias. Providers with little baseline knowledge of Neo-melubrina may have had less interest in participating in the study than those who were familiar with the medication. Given the relatively low response rate, our results may not be generalizable to all providers in San Diego. Another limitation to the study involves the exclusive use of the trade name Neo-melubrina in our questionnaire. Although this is the most common local trade name, pyrazolone analgesic or antipyretic drugs are also known to be marketed under names such as Dolo-tiaminol and Beserol. Clinicians trained in other regions of the country, although not familiar with the name Neo-melubrina, may have some clinical experience with dipyrone under a different trade name.

Dipyrone use in low-income Hispanic populations is clearly a problem that merits further attention. The use of dipyrone may not be limited to low-income persons, and investigation into its use by those in different socioeconomic classes is warranted.

An awareness of foreign medications should not be limited to cities bordering other countries, and we have listed a few resources for identifying unfamiliar medications (see box). Providers in all settings are likely to encounter patients who travel to other countries or who have relocated to the United States and who may, therefore, also be at risk of obtaining potentially harmful medications. Inquiry regarding nonprescription use of foreign medications is important in all clinical settings.

Resources for the identification of unfamiliar medications

Diccionario de Especialidades Farmaceuticas. 24th ed. Bogota, Colombia: PLM International; 2000.

This yearly publication is analogous to the Physicians' Desk Reference in the United States. It lists several thousand pharmaceutical products available in Mexico and Latin America, along with their usages and adverse effects. It is published in Spanish.

Martindale: The Complete Drug Reference (previously known as *Martindale: the Extra Pharmacopoeia*). 32nd ed. London: Pharmaceutical Press; 1999.

This reference, published every 3 years, is an inclusive list of drugs used throughout the world and identifies medications by approved names, synonyms, and chemical names. Included are indications for usage, adverse effects, and information on usage in different regions of the world.

The PDR for Herbal Medicines. 1st ed. Montvale, NJ: Medical Economics; 1998.

This new companion to the PDR helps health care providers identify a wide variety of complementary and alternative medicines, with their common usages and side effects.

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capsule

The number of uninsured Americans is growing

Complaints about Britain's NHS are growing exponentially but universal coverage has its merits. In the US, population survey data show that the number of uninsured Americans is growing (*Health Affairs* 2001;19:188-196). An estimated 17% of children and 19% of adults are uninsured with the highest rates being seen in black non-Hispanic ethnic groups.